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# Creatinine Clearance in Clinical Medicine

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• **Clearance of endogenous creatinine offers a reliable clinical means of determining quantitative renal damage. The rate of clearance ($C_{cr}$) is obtained by relating the amount of creatinine filtered by the glomerulus per unit of time to the concentration of creatinine in the serum. The technic is simple and practical for routine use.**

**Since 1948, the creatinine clearance determination has been used extensively at the University of California Medical Center for the evaluation of renal function. The present report reviews our selected experience with this procedure during the past 14 years. Clinical examples are used to show that the $C_{cr}$ is a more accurate index of glomerular filtration than the concentration of any of the nonprotein nitrogen components of the blood.**

CLEARANCE OF ENDOGENOUS CREATININE gives a reliable approximation of the glomerular filtration rate as measured by inulin clearance.[4,7,9,21,26] Inulin clearance, although generally accepted as the most accurate index of glomerular filtration,[25] is technically complicated and impractical for clinical use. In contrast, the procedure for determining the rate of creatinine clearance ($C_{cr}$) is simple and can be carried out in any clinical laboratory.

During the past 14 years, the creatinine clearance determination has been used at the University of California Medical Center for the evaluation of renal function in patients with and without kidney disease. The technique we use and the normal standards established for healthy men and women were reported in 1951.[12] Recently, studies in this and other centers have provided further data on the range of normal values and the influence on the $C_{cr}$ of various factors such as sex,[9,26] age,[6,27] and pregnancy.[24] Experience during this period also showed the superiority of the $C_{cr}$ in assessing renal impairment, compared with the concentration of urea nitrogen, nonprotein nitrogen or creatinine in the blood. The present report reviews these findings from a clinical standpoint, illustrating the advantages of the $C_{cr}$ by brief case histories.

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## ENDOGENOUS CREATININE CLEARANCE

### Procedure

The rate of endogenous creatinine clearance is derived by relating the amount of creatinine filtered by the glomerulus per minute to the serum creatinine concentration. The determination requires a carefully timed urine collection and a single blood specimen (the patient need not be fasting).[1] Generally, we use a 12-hour specimen of urine collected overnight (from 7 p.m. to 7 a.m.). The collection

may be started at any time of the day, however, and the collection period may vary from 20 minutes to 24 hours. For short collection periods, complete emptying of the bladder, adequate urinary flow and accurate timing are requisite. When the volume of urine obtained is less than normal (approximately 1,500 ml. per 24 hours), incomplete collection or poor hydration should be suspected. Urine obtained by cystoscopy and ureteral catheterization may be used for measuring the $C_{cr}$ of each kidney. If urinary flow is adequate, a 20-minute specimen from each kidney is sufficient for this purpose. The same specimens may be used for measuring the ratio of sodium to creatinine in the urine from each kidney,[2] or for other modifications of the Howard test for the detection of unilateral renal disease.

After the collection of specimens, the volume of urine is measured. The concentrations of creatinine in urine and serum are determined according to the alkaline-picrate method of Folin and Wu, as modified by Peters.[20] The clearance rate is then calculated from the creatinine concentrations and urine volume by the standard clearance formula.[21] The value obtained is corrected to 1.73 square meters of body surface area.

#### Normal Values: Range and Variations

Normal values for this method were established by studies on healthy adult subjects.[12,26] The normal range of $C_{cr}$ is 72 to 141 ml. per minute in men and 74 to 130 ml. per minute in women. Normal serum creatinine concentrations range from 1.0 to 1.6 mg. per 100 ml. in men and from 0.8 to 1.4 mg. per 100 ml. in women. As the serum creatinine concentrations of men and women differ significantly,[9] a single range of normal cannot be used for both sexes.

In some laboratories, serum creatinine concentrations ranging from 0.8 to as high as 2.0 mg. per 100 ml. are considered normal for both men and women. Concentrations as low as 0.4 per 100 ml. have been found in healthy children and as low as 0.6 mg. per 100 ml. in healthy women. The values in the higher range, however, date from the time visual colorimetry was used and are erroneous by present standards. In our experience, a concentration of 2 mg. or more per 100 ml. in either sex is always indicative of impaired renal function as evidenced by a decrease in $C_{cr}$. Conversely, as will be shown, serum creatinine concentrations within normal limits are sometimes found in patients with fairly severe renal insufficiency.

The $C_{cr}$ varies normally with age. It can be used as an index of glomerular filtration in children aged three years or more. After the age of three, or in some infants as early as one year, the $C_{cr}$ reaches the adult range.[16,27] For comparison with standards established for adults, the values obtained in children must be corrected to equivalent body surface area. After the age of 30, as reported by Davies and Shock,[6] the glomerular filtration rate begins to decline slowly. In the same report these investigators presented a formula for predicting normal clearance rates according to age.

From the fifteenth to the thirty-eighth week of pregnancy, the glomerular filtration rate is increased 50 per cent, and may remain at this high level for as long as six weeks postpartum.[24] One of our reported cases[13] illustrates the importance of considering such increases in determining the $C_{cr}$ in pregnant women. The patient, a 30-year-old woman in the thirty-sixth week of pregnancy, was admitted to the hospital because of hypertension, edema, excessive gain in weight and proteinuria. The $C_{cr}$ was 81 ml. per minute, serum creatinine concentration 0.9 mg. per 100 ml., blood nonprotein nitrogen 34 mg. per 100 ml. and uric acid 8.1 mg. per 100 ml. One week later, the serum creatinine concentration was unchanged, but the $C_{cr}$ had decreased to 69 ml. per minute. A renal biopsy at that time showed glomerular abnormalities characteristic of pre-eclampsia. Delivery was normal. Five weeks later, when a second renal biopsy showed resolution of the pre-eclamptic glomerular lesions, the $C_{cr}$ had risen to 154 ml. per minute and serum creatinine concentration was 1.1 mg. per 100 ml.

### CREATININE CLEARANCE VERSUS OTHER CLINICAL "RENAL FUNCTION" TESTS

Impairment of renal function is commonly reflected by changes in the blood urea nitrogen and nonprotein nitrogen (NPN) levels. The concentration of these components in the blood, however, is also materially affected by factors such as protein metabolism, amount of protein in the diet, rate of urinary flow and alterations in extracellular fluid volume.[11,21] A low blood urea nitrogen level is found in a variety of conditions, including overhydration and rapid hydration, and in liver disease.[11] Gastrointestinal hemorrhage can increase the concentration of urea nitrogen in the blood through digestion of protein and intestinal absorption of large amounts of nitrogen. The nonprotein nitrogen concentration is similarly affected in such situations, since its major component is urea. The $C_{cr}$, in contrast, is not influenced by such factors, as shown in the following cases.

The effect of dietary protein intake on the $C_{cr}$ and NPN in a woman with relatively stable renal failure is illustrated in Chart 1. A diet containing 100 gm. of protein daily resulted in a rise in NPN from 89 to 180 mg. per 100 ml. When the amount of dietary protein was decreased to 40 gm. daily, the NPN dropped to 59 mg. per 100 ml. These changes in NPN were not reflected in the $C_{cr}$, which re-

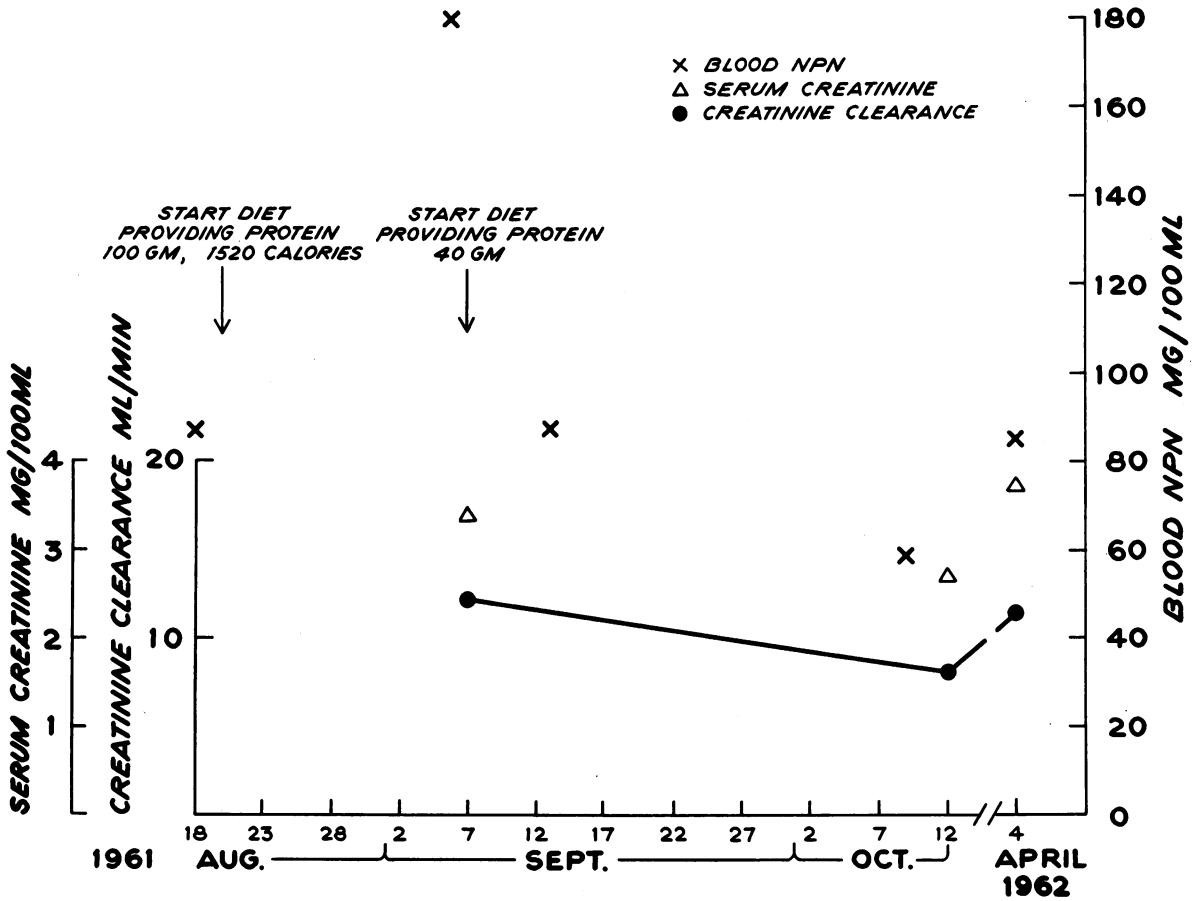


Chart 1.—Results of tests in a woman with relatively stable renal failure during periods of high and low dietary protein intake. Alteration in amount of protein in diet resulted in striking change in NPN, while $C_{cr}$ remained approximately unchanged.

mained relatively unchanged. In another patient, a 55-year-old man, acute tubular necrosis (lower nephron nephrosis) developed after transurethral resection. Chart 2 shows the rapid return of the NPN to normal after diuresis, although glomerular function, as judged by the $C_{cr}$, was still significantly impaired. In a third patient, a 51-year-old man with the milk-alkali syndrome,[10] renal function improved greatly after gastric resection and omission of Sippy powders and milk from the diet. Several years later, he had an episode of gastrointestinal bleeding. As shown in Chart 3, intestinal absorption of blood resulted in a disproportionately high NPN, whereas the $C_{cr}$ remained stable. The transient decrease in the $C_{cr}$ during a second severe hemorrhage into the bowel probably reflected inadequate renal perfusion.

The serum creatinine concentration, unlike the blood urea nitrogen and NPN levels, is relatively unaffected by protein intake or urine volume. It does not provide an accurate index of glomerular function, however, unless related to urinary creatinine excretion.[7,9,16,17,26] The unreliability of the serum creatinine level alone as an index of renal impairment is shown by the data listed in Table 1. The records of ten patients with renal lesions were selected from the files of the Renal Service. In each a low $C_{cr}$ (less than 70 ml. per minute) indicated some degree of renal impairment, although the serum creatinine level was normal or near normal. To determine the validity of the creatinine clearance values, inulin clearance determinations were performed. As shown in Table 1, the inulin clearance rate in all ten cases confirmed the presence of renal impairment as indicated by a low $C_{cr}$.

The table also shows the degree of discrepancy that may exist between the serum creatinine and creatinine clearance values. For example, in Case 5, a low $C_{cr}$ of 31.9 ml. per minute was associated with a serum creatinine level only slightly higher than normal (1.7 mg. per 100 ml.). In Case 6, the clearance rate was 66 ml. per minute, over twice the $C_{cr}$ in Case 5, yet the serum creatinine level was approximately the same (1.9 mg. per 100 ml.).

Another example of significantly reduced creatinine and inulin clearance rates in association with normal serum creatinine levels is shown in Chart 4.

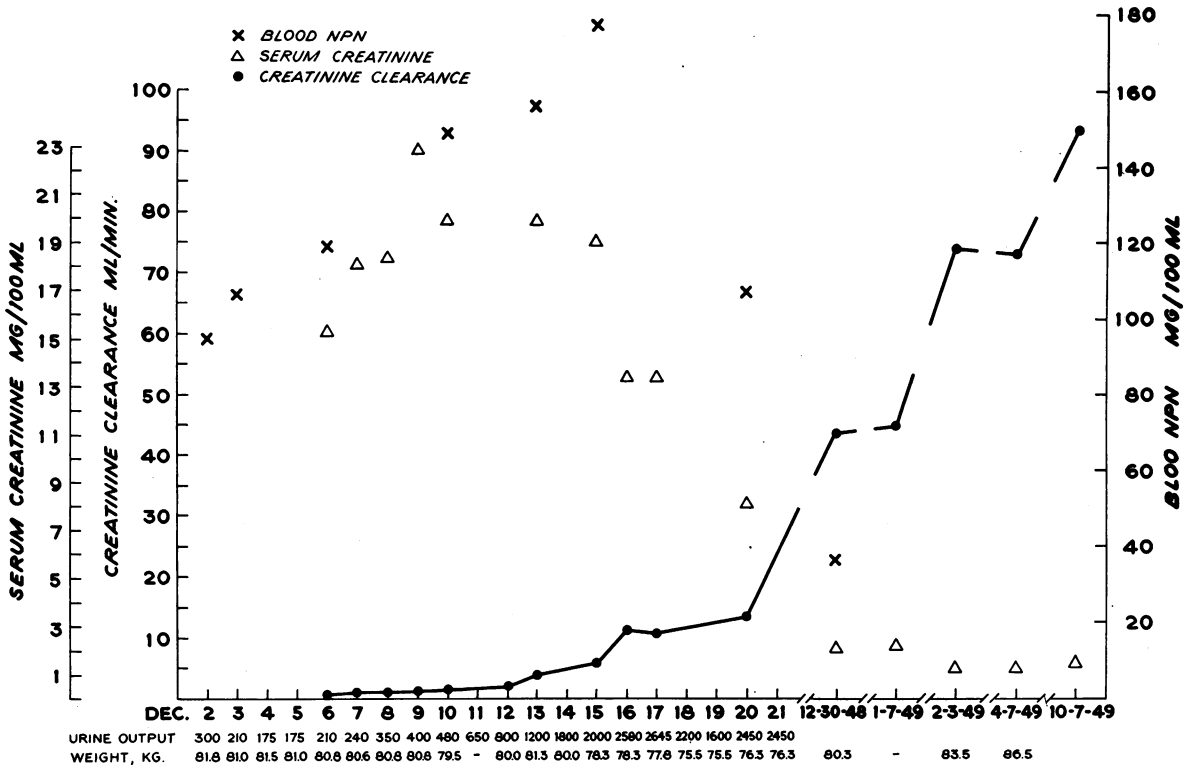


Chart 2.—Results of tests in a man recovering from acute tubular necrosis. After diuresis, NPN returned rapidly to normal levels, although renal function as measured by $C_{cr}$ was still significantly impaired.

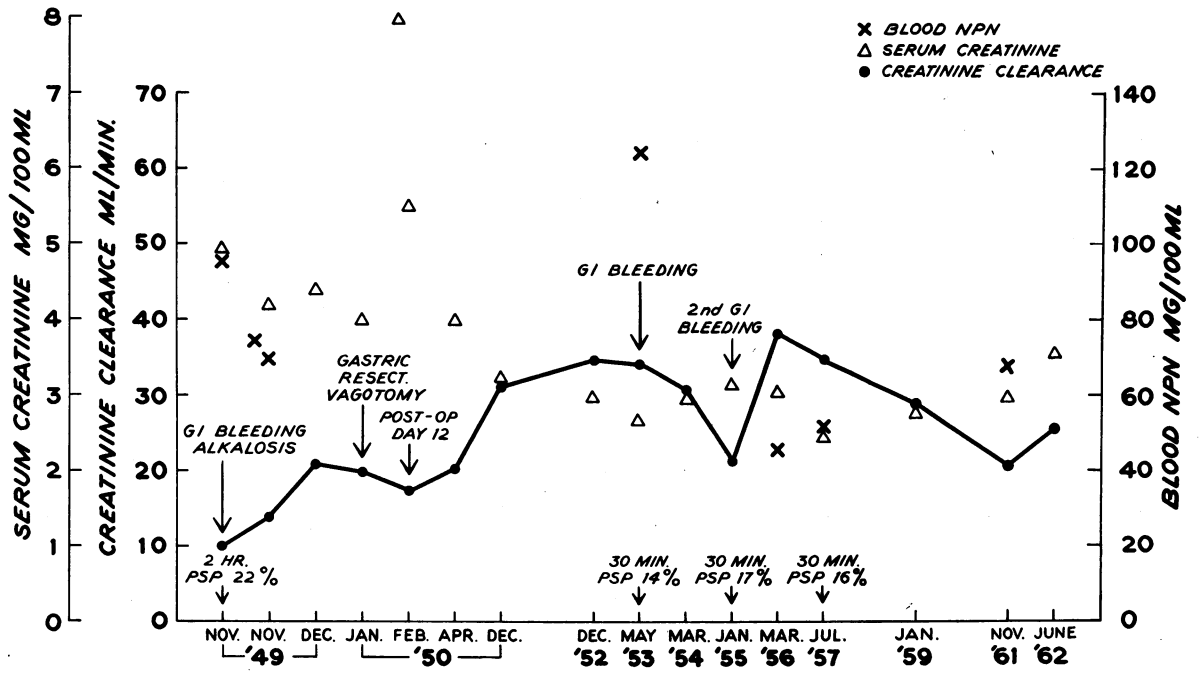


Chart 3.—Results of tests in a man with renal failure during gastrointestinal hemorrhage. During first episode of bleeding NPN rose, probably owing to intestinal absorption of blood, whereas $C_{cr}$ remained stable. Temporary decrease in $C_{cr}$ during second hemorrhage probably reflected inadequate renal perfusion.

TABLE 1.—*Accuracy of Creatinine Clearance Rate ($C_{cr}$) Compared with Serum Creatinine as an Index of Glomerular Filtration Rate (as Established by Inulin Clearance ($C_{in}$))*

| Case No. | Sex | Age | Diagnosis | Serum Creatinine mg./100 ml. | Clearance Creatinine ml./min. | Clearance Inulin* ml./min. | Ratio $C_{cr}/C_{in}$ |
|---|---|---|---|---|---|---|---|
| 1 | M | 16 | Congenital heart disease | 0.9 | 57.5 | 62.5 | 0.92 |
| 2 | M | 37 | Acute glomerulonephritis | 1.2 | 58.0 | 62.5 | 0.93 |
| 3 | M | 42 | Acute glomerulonephritis | 1.2 | 69.0 | 63.0 | 1.10 |
| 4 | M | 19 | Nephrotic state | 1.3 | 63.8 | 56.3 | 1.13 |
| 5 | M | 70 | Right kidney absent, diabetes mellitus | 1.7 | 31.9 | 34.8 | 0.92 |
| 6 | M | 35 | Chronic glomerulonephritis | 1.9 | 66.0 | 52.0 | 1.27 |
| 7 | F | 15 | Chronic glomerulonephritis | 1.1 | 52.0 | 52.0 | 1.00 |
| 8 | F | 42 | Renal tuberculosis | 1.2 | 48.0 | 60.0 | 0.80 |
| 9 | F | 78 | Mild nephrotic state, arteriosclerosis | 1.4 | 43.0 | 47.0 | 0.91 |
| 10 | F | 79 | Healed pyelonephritis, nephrosclerosis | 1.4† | 43.0 | 47.0 | 0.91 |

*Inulin clearance was performed by standard technics[25]; serum and urine concentrations were determined by the method of Roe, Epstein and Goldstein.[22]

†Nonprotein nitrogen was 35 mg. per ml.

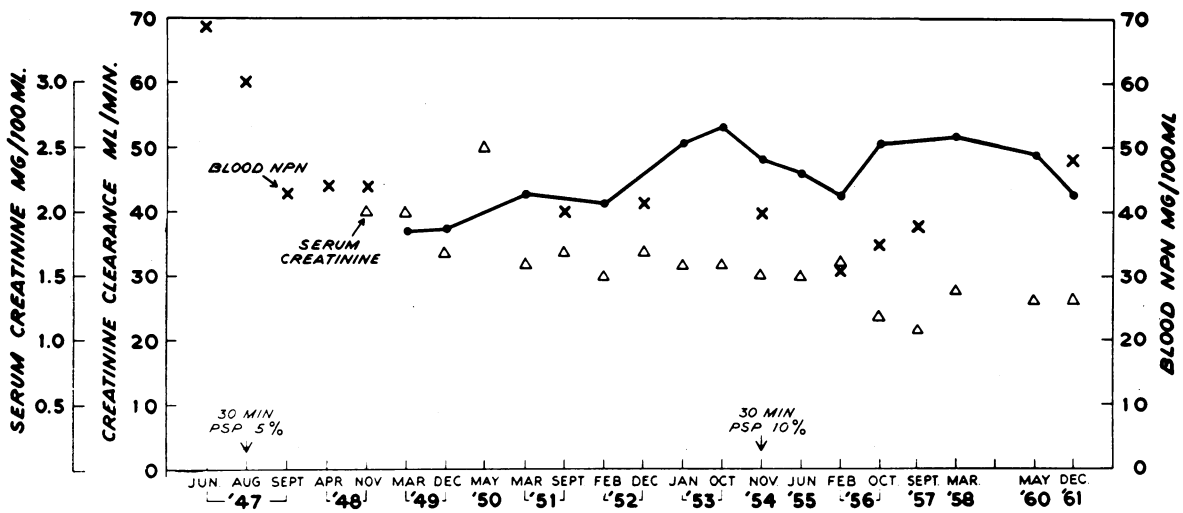


Chart 4.—Results of tests in a woman with chronic pyelonephritis and hypertension. After chemotherapy blood pressure returned to normal, and $C_{cr}$ gradually increased to 45 to 55 ml. per minute, a glomerular filtration rate of roughly half normal. During ensuing years, $C_{cr}$ did not rise above 55 ml. per minute, whereas NPN and serum creatinine levels were frequently normal.

The patient, a 65-year-old woman, had chronic pyelonephritis manifested by hypertension (blood pressure 170/100 mm. of mercury), proteinuria, bacteriuria and pyuria. Before treatment, the $C_{cr}$ was 35 ml. per minute. Chemotherapy resulted in bacteriologic and clinical cure, with disappearance of symptoms and return of blood pressure to normal (130/80 mm. of mercury). During the next five years, renal function returned to about half normal as indicated by a $C_{cr}$ of 45 to 55 ml. per minute, and the patient became and remained free of proteinuria. Although the $C_{cr}$ has remained below 55 ml. per minute since that time, both serum creatinine and blood NPN levels have frequently been within normal limits. The patient has remained asymptomatic, and a recent determination with diet unrestricted showed an NPN of 35 mg. per 100 ml.

The phenolsulfonphthalein (PSP) test is an index of renal plasma flow and tubular excretion. Although a renal lesion may affect both glomerular and tubular function, the degree of involvement is not necessarily the same. The PSP test is therefore a valuable adjunct to the creatinine clearance determination. However, we have found that in severe renal failure as indicated by a $C_{cr}$ below 20 ml. per minute, the amount of PSP excreted is usually too small for accurate measurement. Intravenous urography has a similar disadvantage at this low level of renal function, in that the dyes used are likely to be insufficiently concentrated for adequate visualization of the calyceal systems.

### VALUE OF CREATININE CLEARANCE IN PROGNOSIS

In chronic renal failure, the clinical manifestations are not necessarily well correlated with biochemical changes. We have found, however, that a $C_{cr}$ below 30 ml. per minute is often accompanied

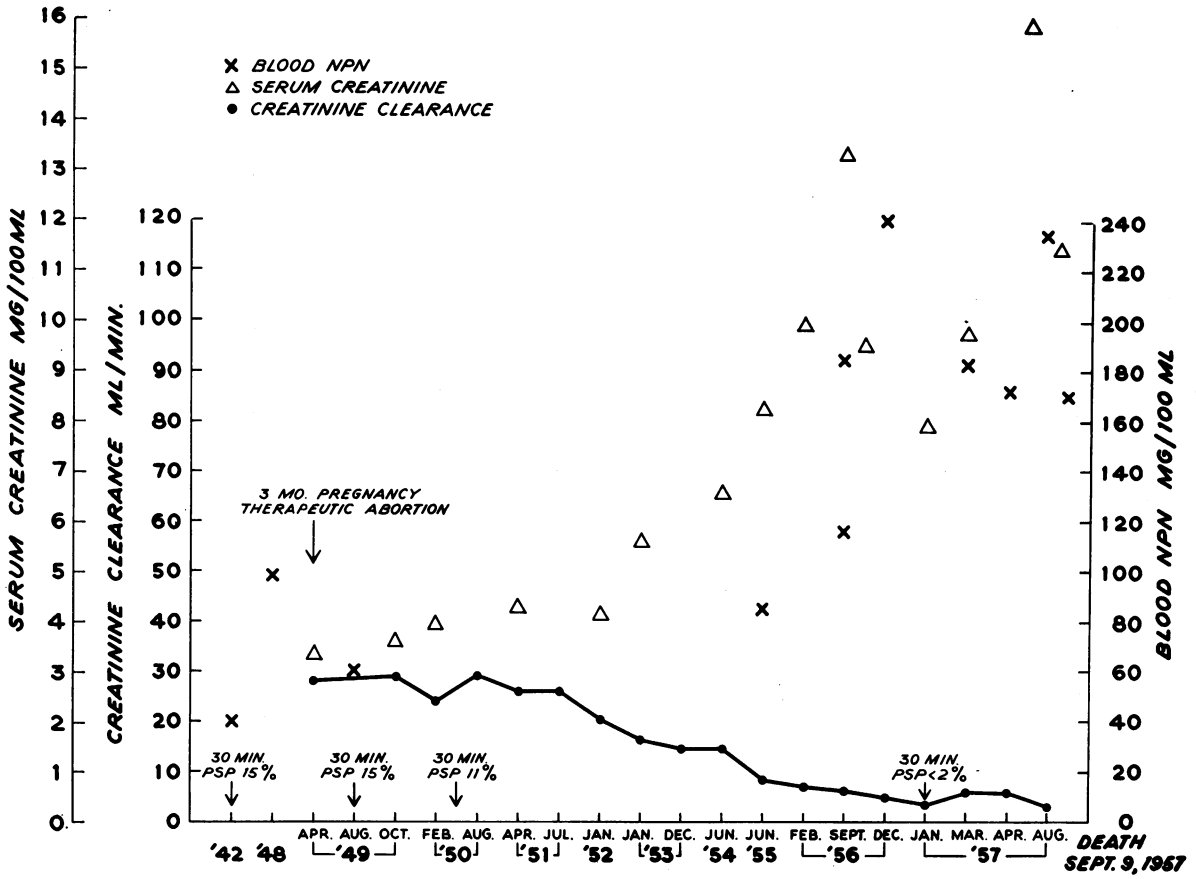


Chart 5.—Results of tests in a woman with chronic glomerulonephritis without hypertension, leading to death in eight years. Slow, regular decline in renal function was accurately reflected only by decrease in $C_{cr}$.

by weakness, fatigability, anemia and electrolyte disturbances. In general in such cases, the prognosis is poor. A further decrease in $C_{cr}$ to 10 ml. per minute or below is associated with an increased incidence of signs and symptoms. If this low rate of clearance persists, the prognosis is very poor. The findings in 21 cases of fatal chronic renal disease[26] illustrate this point. In 17 of the 21 patients, repeated determinations showed a $C_{cr}$ persistently below 10 ml. per minute. Of these, only two patients were alive nine months after the $C_{cr}$ had dropped to this low level. The outcome in chronic renal disease, however, seems to depend not only on the rate of glomerular filtration but also on the rate of change. In chronic renal insufficiency, a rapid decline in $C_{cr}$ indicates a short survival time. If the patient has hypertension as well, the time of survival is likely to be even shorter.

The following examples show the value of the $C_{cr}$ in determining prognosis. A 36-year-old woman had chronic glomerulonephritis without hypertension, leading to her death eight years later. During the eight-year-period, as shown in Chart 5, a slow, steady decrease in $C_{cr}$ was the only accurate laboratory evidence of the progressive course of disease. Another patient, a 43-year-old man, had pyelonephritis manifested by hypertension as a complication of polycystic kidney disease. Intensive chemotherapy resulted in bacteriologic cure and an increase in $C_{cr}$ from 6 to 28 ml. per minute (Chart 6). As hypertension persisted and became worse despite treatment with reserpine and hydralazine, the $C_{cr}$ showed a progressive, parallel decrease. As can be seen in Chart 6, the values obtained for NPN remained approximately the same when the $C_{cr}$ showed a decided change, from 6 ml. per minute to 28 ml. per minute. Thus, even when the bacterial infection was suppressed, the NPN did not accurately reflect changes in renal function.

### USE OF CREATININE CLEARANCE IN ASSESSING HYPERTENSIVE THERAPY

Because of the injurious effects of hypertension on kidney function,[18] treatment with antihypertensive drugs seems especially indicated in hypertensive patients with impaired renal function. Yet caution must be used in administering such agents, particularly if severe renal insufficiency is present.

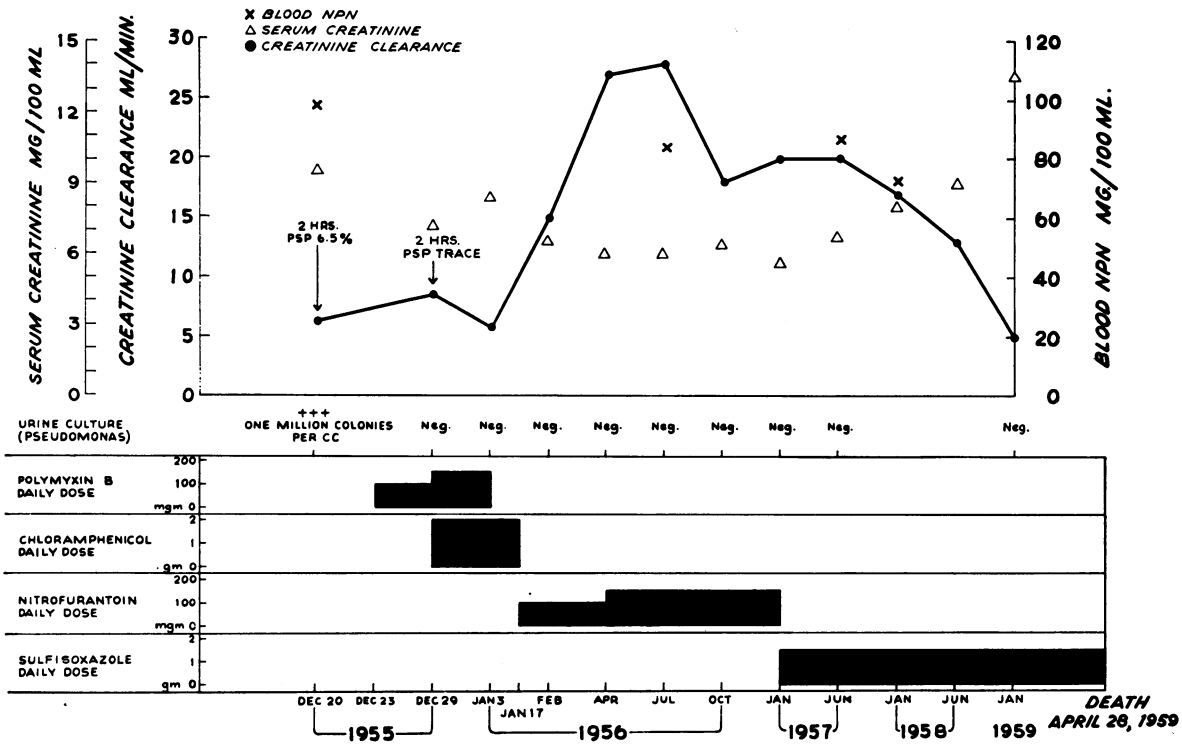


Chart 6.—Results of tests in a man with polycystic renal disease, pyelonephritis and hypertension. Initial improvement after chemotherapy was followed by persistent, progressive hypertension and renal insufficiency, as indicated by decrease in $C_{cr}$.

In hypertensive patients with a $C_{cr}$ below 30 ml. per minute, rigid restriction of dietary sodium or administration of saluretic drugs may cause electrolytic depletion, especially of sodium and potassium, tending to promote renal failure.[15] In such patients, the use of sympatholytic drugs, such as hexamethonium and mecamylamine, often results in further depression of renal function, and occasionally even in anuria. We have encountered few such problems with guanethidine, reserpine and hydralazine. A new antihypertensive agent, alpha methyl dopa,* appears promising for the treatment of hypertensive patients with renal failure, since it usually does not result in further impairment of renal function.[5,8,14,19] Dollery and Harington,[8] however, observed increased azotemia in some of their patients treated with this drug.

Because the blood urea nitrogen and NPN levels do not provide an adequate measure of the glomerular filtration rate, we strongly urge the use of the creatinine clearance determination in assessing the effects of antihypertensive drugs in patients with renal insufficiency. The $C_{cr}$ should be determined before such treatment is begun and at weekly intervals thereafter, or more often if indicated, until it is established that the glomerular filtration rate is not significantly decreased.

*It should be cautioned that alpha methyl dopa, because it is easily oxidized, tends to interfere with the determination of urinary and serum creatinine by the alkaline-picrate method.

### LIMITATIONS OF CREATININE CLEARANCE DETERMINATION

Determination of the $C_{cr}$, like all laboratory tests, is subject to technical error. Both De Wardener[7] and Brod[3] have described a number of factors that lead to erroneous rates of clearance or interfere with the satisfactory performance of clearance determinations.

We, like others, have found that the $C_{cr}$ may be misleading in certain clinical conditions. For instance, even when there is complete loss of function of one kidney, the glomerular filtration rate may be within normal limits. Such cases of unilateral kidney disease may not be detected by the $C_{cr}$, or by other tests designed to measure total renal function. Even when both kidneys are functioning normally, partial obstruction of the lower urinary tract or of both upper tracts is likely to be reflected by a low $C_{cr}$, suggesting primary renal disease to the unwary. In severe anemia, shock or dehydration, renal vascular obstruction or congestive heart failure, circulatory renal failure can lead to a decrease in function in otherwise normal kidneys, resulting in low $C_{cr}$.

Despite these limitations, the creatinine clearance determination has obvious advantages over the other

commonly used "renal function" tests. Schreiner and Maher[23] stated that they found the $C_{cr}$ "an extremely useful tool, perhaps the single most valuable one, in the serial follow-up of patients with chronic renal disease." We agree, and would add that it is similarly useful for the long-term observation of patients with hypertension, acute renal disease or systemic disease implicating the kidneys, as well as a screening test for the early detection of renal insufficiency. The $C_{cr}$ is also useful in evaluating the effects of treatment with potentially nephrotoxic drugs. Winn[28] has found the $C_{cr}$ much more informative than the blood urea nitrogen determination in following patients with coccidioidomycosis during treatment with the highly nephrotoxic drugs amphotericin B.

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